Attenuated Myocardial Vasodilator Response in Patients With Hypertensive Hypertrophy Revealed by Oxygenation-Dependent Magnetic Resonance Imaging

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Background—Oxygen (O_2) homeostasis is central to myocardial tissue functioning, and increased O_2 demand is thought to be satisfied by a vasodilatory mechanism that results in increased blood and O_2 delivery. We applied blood oxygenation level–dependent (BOLD) MRI in conjunction with vasodilatory stress to index the ability to augment intramyocardial oxygenation in hypertensive hypertrophy, the primary cause of heart failure.

Methods and Results—Nine healthy controls and 10 hypertensive subjects with moderate-to-severe hypertrophy underwent imaging on a 1.5 T clinical scanner. The dipyridamole-induced change in the apparent transverse relaxation rate, R2*, which correlates with hemoglobin oxygenation, was -5.4 ± 2.2 s^{-1} (95% CI, -4.0 to -6.8 s^{-1}) in controls compared with -1.7 ± 1.4 s^{-1} (95% CI, -0.8 to -2.6 s^{-1}) in hypertensive patients ($P=0.0003$).

Conclusions—Patients with hypertensive hypertrophy demonstrate an impaired ability to increase intramyocardial oxygenation during vasodilatory stress, as indexed by BOLD MRI. The capacity to image vascular function with BOLD MRI may advance the understanding of the development of ventricular dysfunction in hypertension. **(*Circulation*. 2001; 104:1214-1217.)**

Key Words: magnetic resonance imaging ■ hypertension ■ hypertrophy ■ angiotensin-converting enzyme inhibitors ■ endothelium, vascular

Hypertension is a major public health concern worldwide, and the complication of myocardial hypertrophy carries an independent risk for cardiovascular morbidity and mortality.[1] Due to advances in echocardiography, the estimation of structural change in hypertension is now established. Studies using catheterization[2] and positron emission tomography[3] have documented reductions in vasodilator function, implying a reduced availability of oxygen (O_2) to satisfy myocardial energy demand. However, because hypertensive patients are often otherwise healthy, catheterization methods are of limited use in the clinical evaluation of such patients and positron emission tomography is not widely available and requires the use of radioactive tracers.

Thus, with the advent of clinical trials demonstrating the benefits of newer vascular-targeted therapies in reducing cardiac events in subjects at risk,[4] the development of a noninvasive oxygenation-sensitive imaging method to evaluate intramyocardial vasodilator function could potentially advance the functional assessment of hypertensive heart disease.

Blood oxygenation level–dependent (BOLD) MRI is based on sensitivity to deoxyhemoglobin, the body's own paramagnetic contrast agent. Thus, stimuli that change the blood O_2 saturation result in the alteration of magnetic susceptibility, affecting water proton spins in and around blood vessels, which manifests as signal changes detected by MRI methods that are sensitive to field inhomogeneities.

Canine studies have shown a linear relation between the intramyocardial BOLD MRI response to reactive hyperemia and coronary flow-velocity change.[5] We applied BOLD MRI with pharmacological stress in patients with hypertensive hypertrophy, a condition with known global vascular function abnormalities.

Methods

Physiological Rationale

The BOLD mechanism is fundamentally dependent on the deoxyhemoglobin concentration in an image pixel and the blood volume fraction, both of which affect the MRI apparent transverse relaxation rate, R2*. Through the Fick principle, which describes the conservation of O_2, the deoxyhemoglobin concentration depends on the balance between the O_2 metabolized by the tissue and the O_2

Received May 21, 2001; revision received July 18, 2001; accepted July 20, 2001.

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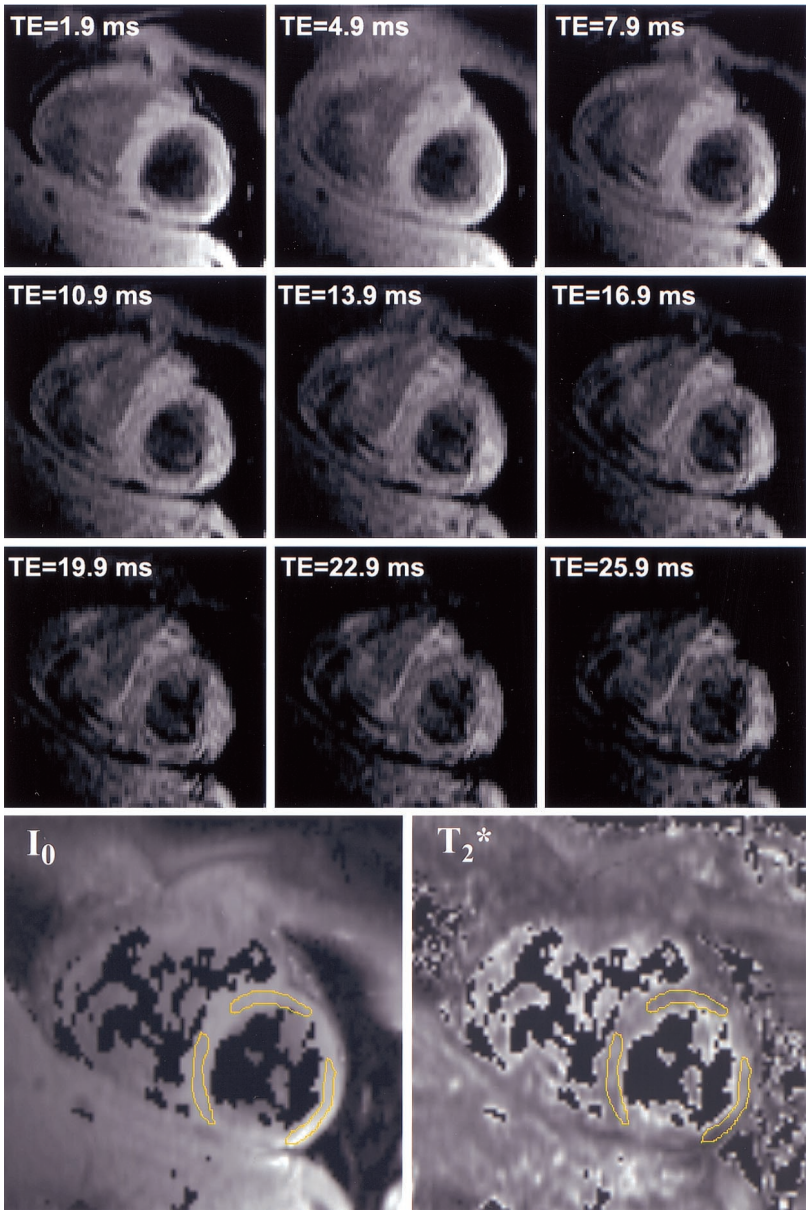

Figure 1. Cardiac short-axis section showing the multiple echo-time raw data and their derived extrapolated TE=0 (I_0, anatomic) and T_2^* (oxygenation-sensitive) images, with typical regions of interest.

delivered by flow. Thus, changes in R2* due to hemodynamic and/or metabolic perturbations can be related to alterations in blood volume, flow, and metabolism.[6]

Dipyridamole was chosen as the stress agent because it elicits a response that primarily results in an increase in flow and an order of magnitude smaller increase in blood volume with very little effect on metabolism.[7] Therefore, the change in R2* due to dipyridamole is determined by changes in blood oxygenation, which result primarily from a change in flow and O_2 delivery. The normal response to dipyridamole is a decrease in R2*, occasioned largely by a decrease in deoxyhemoglobin due to luxury blood flow.

Subjects

Ten male patients aged 34 to 47 years (mean, 43±4 years) with hypertension (documented by blood pressure >140/90 mm Hg or who were being treated with antihypertensive medications) were enrolled in this study, which was approved by our Institutional Review Board. Written, informed consent was obtained. All patients had left ventricular (LV) hypertrophy, with LV mass ranging from 231 to 428 g (mean, 299±68 g); mass was measured using the 2D echocardiography 5/6 area-length method. Patients with a history of aortic stenosis or diabetes mellitus were excluded. None of the patients had angina, dyspnea, or ECG evidence of coronary artery disease. Seven patients had normal cholesterol levels, and the remaining 3 had levels in the range between 200 and 239 mg/dL (borderline elevated). Eight patients had a history positive for tobacco within 3 months.

Nine healthy subjects (3 women; aged 25 to 47 years; mean age, 33±7 years; $P<0.05$) who had no history of hypertension, diabetes mellitus, or heart disease and who were not on medications were recruited. Three had a positive tobacco history ($P<0.05$ by χ^2). All controls had a normal blood pressure and normal diastolic regional wall thickness measurements by MRI. Patients were withdrawn from medications that affect cardiac performance for a period of 24 hours preceding MRI. Caffeine intake and smoking were also temporarily stopped for at least 4 to 6 hours. No subject was taking theophylline or xanthine derivatives.

MRI Protocol

A segmented, gradient-echo sequence with multiple echoes was used to acquire a set of 9 images with echo time (TE) values of 2 to 26 ms on a 1.5T Signa (GE Medical Systems). A single short-axis image section was acquired in a breathhold, triggered by 24 heartbeats, to estimate the apparent transverse relaxation time (T2*=1/R2*) of the myocardium. Ninety-degree saturation pulses and signal-crushing gradients were applied to basal and apical slabs, allowing time for

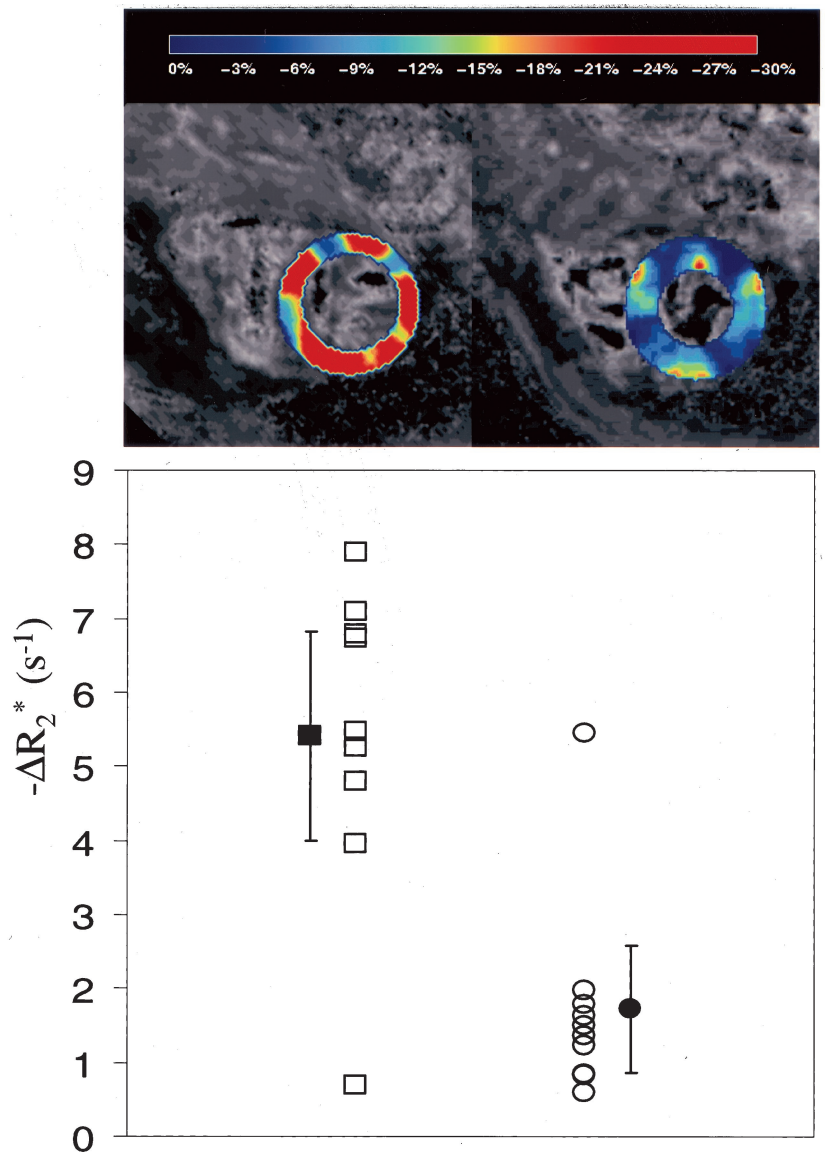

Figure 2. Global BOLD functional parameter (ΔR_2^*) for all controls (left; □) and patients (right; ○), with mean and 95% CI. Parametric images, using a continuous color scale (greatest, red; least, blue) map the fractional R2* change in a representative control and patient. Baseline variability manifests as peripheral defects in the control.

saturated ventricular blood to enter the imaging slice. Inversion pulses were also applied after imaging each segment to further reduce flow artifacts. The imaging sequence comprised 5 excitations per heartbeat, which were delayed to occur during a 140 ms diastolic window for each cardiac cycle (pulse sequence repetition time, 28 ms; flip-angle, 30°; bandwidth, ±62.5 kHz; 256×120 image pixels; field-of-view, 400×400 mm with 1.56×3.33×10 mm resolution). T2* acquisition was repeated at least 7 times to establish a baseline. Dipyridamole was then administered peripherally (0.56 mg/kg total over 4 minutes), and stress images were acquired approximately every minute for 20 minutes. The series of T2* images constituted a dataset over baseline and stress epochs. Pulse and blood pressure were remotely monitored (Omega 1400, Invivo Research Labs Inc). Study time was ≈40 minutes.

To gauge hypertrophy, we measured the wall thicknesses in the 3 major vascular territories. Mean wall thickness was correlated with a global BOLD functional parameter.

Data Analysis

Each set of the nine TE images was combined to estimate T2* using a linear fit to a logarithmic plot of the MRI signal as a function of TE (Figure 1). Data from pixels with correlation coefficients of $r<0.95$ were excluded to minimize background noise. Registration was performed to correct for in-plane motion. Regions of interest of fixed size and shape that corresponded to the 3 coronary territories were positioned in the central myocardium and tracked through time. For each region of interest, mean baseline and stress T2* values were computed using at least 7 images. From the mean values, we computed the dipyridamole-induced change in R2* ($\Delta R2^*=\Delta 1/T2^*$). Processing took ≈30 minutes on a Sun UltraSPARC 1 (200 MHz).

As a topographic display of the vasodilator response, for each T2* dataset we computed parametric images defined as the mean R2* of stress images minus the mean R2* of baseline images, normalized by the baseline R2*. For each image comprising the T2* dataset, boundaries were manually prescribed using independent circles, which defined an LV ring. The subset of LV rings corresponding to rest and stress epochs were registered, and mean rest and stress LV rings were computed. The mean LV rings were then coregistered by resampling the pixels of one ring, which was geometrically scaled to fit the other. The final image was not smoothed.

Values are reported as mean±SD. Unpaired 2-sided Student's *t* test and the 95% confidence interval (CI) were calculated. Regional variation of the stress response among the 3 vascular territories was tested using a one-way ANOVA.

Results

There were no significant regional dependencies of ΔR2* among the myocardial territories for either the control or

patient groups, permitting us to pool signal intensity measurements from the 3 vascular territories and, thus, to derive robust estimates for each subject. The SD of the signal intensity of the baseline T2* images in normal subjects was ≈5%, whereas the mean dipyridamole effect-size was 18%, a 3-SD effect.

ΔR2* was lower by a factor of 3 in hypertensive patients (-1.7 ± 1.4 s^{-1}; 95% CI, -0.8 to -2.6 s^{-1}) compared with controls (-5.4 ± 2.2 s^{-1}; 95% CI, -4.0 to -6.8 s^{-1}), a highly significant reduction ($P=$ 0.0003; Figure 2). Parametric images revealed a pattern of globally reduced vasodilator response in hypertensive patients (Figure 2).

Mean resting R2* over the 3 regions of interest in hypertensive patients (36 ± 11 s^{-1}) was not significantly different from that of controls (36 ± 9 s^{-1}). A trend suggesting an inverse relation between mean wall thickness and the global ΔR2* in patients did not achieve significance ($r=-0.6$, $P=0.1$).

Discussion

We demonstrated an ≈3-fold reduction in the oxygenation-dependent response to dipyridamole using BOLD MRI in hypertensive patients with LV hypertrophy. The magnitude of the reduction of the BOLD-indexed vasodilator response is in accord with the measured reduction in vasodilator function reported in several hypertension series.[2] However, because the present hypertensive cohort was asymptomatic, invasive measurements were not feasible.

Reduced vasodilator reserve has been reported in hypertensive patients, both with and without myocardial hypertrophy. The relation of the BOLD abnormality to hypertrophy severity has not been resolved.

Although first-pass, contrast agent–enhanced MRI can assess vasodilator reserve, the efficient extraction of agent during the first-pass results in a complex dependence of the perfusion parameter on flow, blood volume, and extraction fraction. Further, because of the transient effect of extracellular agents, separate baseline and stress administrations are required. The BOLD method permits robust observations without the inconvenience and additional costs of extrinsic agents.

The parametric images document a typical global reduction in the hypertensive cohort. This could be the result of severe triple vessel coronary artery disease. However, this is unlikely because none of the patients had symptoms, ECG abnormalities, or a history that would suggest underlying significant epicardial disease.

Although the present method entailed single-slice acquisition, this should not affect the outcome because the vascular abnormality in hypertension is believed to be generalized. Improved scanning efficiency will permit multislice imaging.

Even in the controls, the parametric images manifested areas of nonuniformity. This could be ameliorated by increasing the signal-to-noise ratio, for example, by using advanced cardiac-specific detectors or increasing the magnetic field strength and/or by using T2 (in lieu of T2*) acquisitions, which may also permit absolute physiological quantification.[6]

Hypertension plays a fundamental role in conferring heart disease risk for millions worldwide. Hypertensive hypertrophy is the primary precursor of congestive heart failure, even in the absence of coronary artery disease.[1] The mechanism of progression to congestive heart failure is poorly understood, but vascular factors, modifiable by interventions with angiotensin-class drugs, are thought to play a major role.[8] We identified, with BOLD MRI, a reduced capacity to augment intramyocardial oxygenation in hypertensive hypertrophy. This deficiency might underlie the energy-dependent abnormalities that are thought to contribute to ventricular dysfunction. BOLD MRI, with its intrinsic sensitivity to the dynamic supply-demand balance of critical myocardial O_2 substrate, can potentially provide new insights into the pathophysiology and management of hypertensive heart disease.

Acknowledgments

Supported by grant KO1 HL03837 (to G.M.B.). Dr John Eng assisted with statistics, and Drs Stanley S. Siegelman, Peter C. van Zijl, and Aleksander S. Popel provided critical comments.

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